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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,589	PRUSINER ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *16-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☒ Claim(s) *1 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/04;9/1/05;9/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are presented for examination.

Acknowledgment is made of the present application as a continuation-in-part (CIP) of PCT Application No. PCT/US02/16349, filed May 23, 2002, and claims benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 60/446,712, filed February 11, 2003; 60/329,602, filed October 15, 2001; 60/301,345, filed June 26, 2001; 60/293,705, filed May 25, 2001; and 60/293,771, filed May 25, 2001.

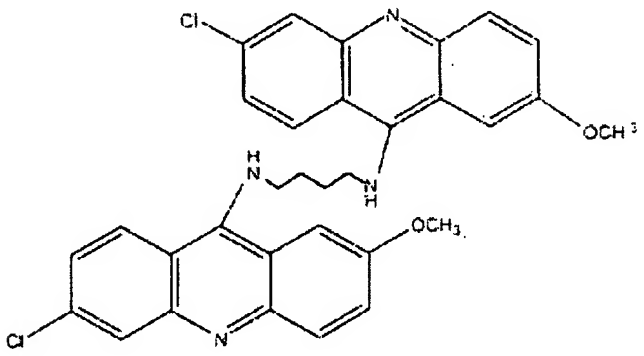
Applicant's Information Disclosure Statement (IDS) filed August 17, 2004 (one page), September 1, 2005 (one page) and September 2, 2005 (one page) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A (three pages total), the Examiner has considered each of the cited references.

Applicant's response filed March 14, 2006 to the requirement for restriction/election dated February 28, 2006 was received and entered into the present application. A supplemental requirement was sent September 22, 2006, to which Applicant filed a response on October 19, 2006. Pursuant to the notice dated December 20, 2006, Applicant's reply of October 19, 2006 was held to be non-responsive. Applicant's response filed December 28, 2006 to the notice of December 20, 2006 was received and entered into the present application. Pursuant to the notice dated March 8, 2007, Applicant's reply of December 28, 2006 was again non-responsive. Applicant's response filed March 19, 2007 was received and entered into the present application, but was again non-responsive. Notice to this effect was sent May 17, 2007, to which Applicant filed a reply on May 24, 2007. A supplemental response was filed on May 25, 2007 correcting an error in the reply of May 24, 2007.

Requirement for Restriction/Election

Applicant's election **with traverse** of the invention of Group I (claims 1-16), directed to a method

of treating a disease resulting from malformed proteins from a mammal comprising administering to said mammal a therapeutically effective amount of a bis-cyclic compound, wherein said bis-cyclic compound is characterized by clearing malformed proteins and by an ability to cross a blood brain barrier of said mammal, in the reply filed March 14, 2006; the election of prion diseases and the specific species of Creutzfeldt-Jakob disease as the species of disease resulting from malformed proteins to be treated, in the replies filed October 19, 2006 and December 28, 2006; and the election of compounds wherein the linking group is defined as group (a) in claim 3 and each "R" attached to the linking group is a quinacrine moiety and the compound is of the structure



, in the replies filed March 19, 2007; May 24, 2007; and May 25, 2007, are each acknowledged by the Examiner.

Applicant traverses the requirement on the grounds that it would not be unduly burdensome to perform a search on all of the claims together in the present application. Applicant further traverses the requirement to elect a single disclosed specie within the genus of "prion diseases", since Applicant asserts that all prion diseases are caused by the same pathogen, i.e., PrP protein, and, therefore, are completely related and searchable in a single search.

Applicant's traversal has been carefully considered in its entirety, but fails to be persuasive.

Applicant is reminded that the instant claims are directly to multiple patentably distinct inventions, namely, methods of treating various diseases resulting from malformed proteins in a mammal and/or clearing malformed proteins from livestock and various embodiments of compositions comprising

bis-cyclic compounds, which are clearly distinct inventions because the compositions as claimed may be used in a variety of therapeutic indications, such as, e.g., Type I diabetes, Creutzfeldt-Jakob disease, multiple myeloma, etc. Additionally, it is noted that claims to compositions are not limited by a particular use and, thus, require various considerations that are not required when assessing method claims for patentability. As a result, search and examination of all of the multiple claimed inventions would be a clear burden upon the Examiner because a comprehensive search and examination of the prior art, both in patent and non-patent literature, would not necessarily result in a complete search and examination of any one or more of the other claimed inventions. In view of the patentable distinction and separate considerations required for each invention, restriction for examination purposes is clearly proper.

Furthermore, since Applicant has failed to provide any evidence or reasoning as to why the search and examination of all of the multiple claimed inventions would *not* be a burden upon the Examiner, the restriction requirement is maintained in view of the reasoning provided in the previous Office Actions of February 28, 2006 and September 22, 2006.

Additionally, though Applicant may have discovered an underlying commonality to the claimed genus of prion diseases, i.e., that they are each related to PrP protein pathogen, "prion diseases" as a genus encompasses a number of diseases that are each distinct in etiology, pathophysiological manifestations and patient population such that a comprehensive search for one prior disease would not necessarily result in a comprehensive search of any one or more other prior disease. Moreover, the finding of a single prion disease, such as, e.g., fatal familial insomnia, would not necessarily anticipate or render obvious a different and distinct prior disease, such as, e.g., chronic wasting disease, particularly because the art does not necessarily recognize all such diseases as being amenable to the same pharmacologic therapies. Lastly, it is further noted that that art may recognize an advantageous use for the compound in achieving the presently claimed objective that is not necessarily tied to its function in clearing "malformed proteins" as alleged by Applicant.

Therefore, for the reasons above and those made of record at pages 2-5 of the previous Office Action dated February 28, 2006 and pages 2-6 of the previous Office Action dated September 22, 2006, the restriction requirement is deemed proper and is hereby made **FINAL**.

Claims 16-28 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 1-15 and such claims are herein acted on the merits.

Objections to the Claims

Claim 1 is objected to for reciting, "...treating disease resulting from malformed proteins from a mammal...". The phrase "disease resulting from malformed proteins from a mammal" is grammatically awkward and fails to clearly set forth whether the malformed proteins are contained *in* a mammal or whether they originated in some manner from a mammal. Appropriate grammatical correction is required.

Claim 9 is objected to for misspelling ---Creutzfeldt--- as "Creutzfeld" in line 7 of the claim.

Objection to the Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at p.36, para.[00132], last line. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. Please reference MPEP §608.01.

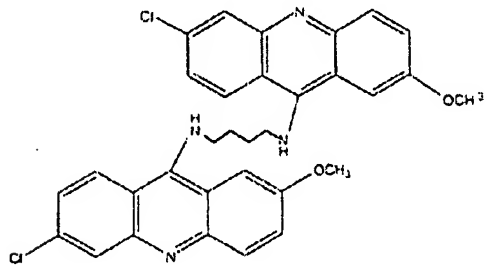
Claim Rejections - 35 USC § 112, First Paragraph, Enablement Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode

contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating (defined as also encompassing the embodiments of prevention, inhibition or relief; see, e.g., p.11-12, para.[0060-0063]; p.25, para.[00100]) Creutzfeldt-Jakob disease in a patient that has, or is at risk for, said disease using the bis-cyclic compound



in a therapeutically effective amount. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The present invention is directed to a method for treating a disease resulting from malformed proteins, i.e., Creutzfeldt-Jakob disease, in a mammal comprising administering to said mammal a therapeutically effective amount of a bis-cyclic compound of the compound presented *supra*, wherein said compound is characterized by clearing malformed proteins and by an ability to cross the blood brain barrier of said mammal. Applicant defines the term "treating" in the following manner:

""Treatment" as used herein covers any treatment of a disease in an animal, particularly a human, and includes:

(a) preventing the disease or symptom from occurring in a subject which may be predisposed to the disease or symptom but has not yet been diagnosed as having it;

(b) inhibiting the disease of its symptom, i.e., arresting development of the disease or its symptoms; or

(c) relieving the disease symptom, i.e., causing regression of the disease or symptom."

Please see Applicant's specification, p.12, para.[0060-0063].

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its fact that an amount of the claimed compound (see structure *supra*), therapeutically effective to treat Creutzfeldt-Jakob disease, could be determined without the need for undue experimentation in the absent of any guidance or direction in the instant specification as to a standard for comparison to determine what is or is not therapeutically effective; what factors are assessed to determine if there has been a therapeutic response; what threshold values must be crossed or reactions must be seen to reasonably conclude that a therapeutic response has been achieved; and what approximate dosage amounts would be reasonable expected to yield a therapeutic response in a subject suffering from Creutzfeldt-Jakob disease.

Moreover, one skilled in the could also not practice the presently claimed subject matter of preventing, inhibiting or relieving the disease or symptoms of the disease of Creutzfeldt-Jakob disease by

administering the claimed compound (see structure *supra*) without undue experimentation because the artisan would not accept on its fact that prevention, inhibition or relied of Creutzfeldt-Jakob disease could actually be achieved given the state of the art at the time of the invention.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

Lack of Enabling Direction to Determine Therapeutically Effective Amounts of the Claimed Agent

The present claims circumscribe a method for treating Creutzfeldt-Jakob disease in a patient comprising the administration of a therapeutically effective amount of the compound described *supra* (see structural formula above). That is, in order to be enabled to practice the present invention, the skilled artisan would be obligated to undertake extensive testing to determine what dosage amounts of the claimed active agent would actually result in a therapeutic effect, since the specification as originally filed fails to provide the skilled artisan with any direction or guidance as to how one of skill in the art would go about determining what dosage amounts would, in fact, be therapeutically effective such that the claimed objective could actually be achieved. Accordingly, the present specification is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Applicant describes various compounds within the scope of the invention, including the one presently claimed and under examination, at pages 13-18 of the instant specification and presents the

following disclosure relevant to the determination of therapeutically effective dosage amounts:

"A range of factors are known to affect dosing including the size, weight, sex, age and condition of the patient. Those skilled in the art will adjust dosing as needed, beginning with smaller doses and increasing gradually while monitoring side effects and the effect of the drug on the disease being treated.

With an oral formulation of a compound such as quinacrine, dosing is generally in an amount of about 100-10,000 mg/day/75 kg of body weight of the animal being treated. Thus, a human dose is about 100-10,000 mg/day, and larger animals are given larger doses in proportion to their weight. It should be noted that the efficacy of a compound on cells is some indication of the potency of the compound. However, some compounds cross the blood-brain barrier more efficiently than others and such is to be considered in dosing.

When quinacrine and chlorpromazine are given in combination, the total dosage is generally the same as for quinacrine alone. That is, 10-10,000 mg/day per 75 kg of body weight. The compounds used in the combination therapy may be applied serially, in any order, or both compounds may be administered at the same time. Preferentially, the combination of compounds is given at the same time to the subject. One of skill in the art would know how to manipulate the ratio of dosages to provide for an optimal result." (p.22, para.[0087-0089])

Applicant further states at page 30, para.[00111]:

"Any suitable dosage can be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the mammal, body weight, and disease being treated. The dosage administered will, of course, vary depending upon known factors, such as the Pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and/or weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired."

However, the specification provides no direction or guidance as to how large or small a quantity is, in fact, effective to reduce PrPSc protein concentration *in vivo*. Though the specification provides exemplary dosage amounts of quinacrine or quinacrine in combination with chlorpromazine, such disclosure fails to provide any direction or guidance to the skilled artisan as to how one would go about determining a comparable dosage amount of the claimed bis-quinacrine compound (see structure *supra*) for use in treating Creutzfeldt-Jakob disease. In other words, the only direction that Applicant has provided for determining an amount effective to achieve a therapeutic effect is for compounds that are not commensurate in scope with what is presently claimed and under examination. Specifically, though the

elected compound under examination may contain, in part, two quinacrine moieties, Applicant has failed to take into account the fact that the two quinacrine moieties are connected via a nitrated alkyl linker and, thus, would have been reasonably expected to differ in the potency and activity of the compound. Furthermore, though quinacrine *per se* may be effective in an amount of 10-10,000 mg/day per 75 kg of body weight, such disclosure fails to provide any basis, evidence or reasoning, as to why the instantly claimed compound would have been equally, or at least substantially similarly, effective in the same amount.

Even if, for the sake of argument, that the dosage amount disclosed as effective for quinacrine *per se* was also effective for the claimed active agent under examination, such disclosure of a dosage amount of 10-10,000 mg/day per 75 kg of body weight does not specifically correlate the claimed active agent and the relative potency of the compound. For example, though the compound may be "effective" in an amount of 10-10,000 mg/day per 75 kg of body weight, Applicant has failed to take into account the potency of the compound and its efficiency in reducing PrPSc protein concentration. In other words, would 10 mg/day per 75 kg body weight be effective to elicit a therapeutic effect? Would it be more effective in reducing PrPSc concentration in an amount of 10,000 mg/day per 75 kg body weight? Additionally, if Applicant fails to define any standard by which to measure the claimed therapeutic effect, how would one of ordinary skill in the art know whether such an amount met the criteria of a "therapeutically effective amount" or not?

Here, in the instant case, even if Applicant had supplied some sort of criteria or standard by which to determine if a compound had a therapeutic effect in a patient suffering from Creutzfeldt-Jakob disease, the specification conspicuously lacks any correlation between the degree of PrPSc reduction and/or inhibition that must occur in order to show some sort of therapeutic benefit to the patient. In other words, it is unclear exactly how much reduction and/or inhibition of PrPSc must take place in order to treat Creutzfeldt-Jakob disease. Is 50% reduction and/or inhibition sufficient? Is 90% reduction and/or

inhibition necessary? Absent any correlation between the function of the PrPSc and the degree to which it must be reduced and/or inhibited in order to confer a therapeutic benefit to the patient, the skilled artisan would have no alternative recourse but the burden of undue experimentation to determine what amounts of the claimed active agent would be therapeutically effective.

The fact also remains that drugs have distinctly different pharmacokinetic profiles of action once administered to a subject. Various processes that affect the activity of a drug once administered are the half-life of the drug, absorption, distribution, any sequestration of the drug that may happen in the body (i.e., into adipose tissue), total body clearance, metabolism and biotransformation (i.e., oxidation, reduction, hydrolysis, conjugation, etc.), activity of cytochrome P-450 enzymes, and excretion of the drug, each step of which affects, at minimum, the serum concentrations, therapeutic index, elimination, and total drug accumulation. In addition, certain factors that affect the activity of a drug are subject-dependent. For example, genetic polymorphisms can affect whether the body can actually metabolize certain drugs; a concomitantly administered drug may stimulate or interact with another drug; the route of administration used and the resultant extent of hepatic metabolism (if oral administration is used); diet; amount administered, since toxic doses can deplete enzymes needed for detoxification; age; gender; and any concomitant medical conditions, such as liver or kidney disease.

Applicant fails to address this unpredictability in the art by presenting any guidance or direction as to how one of ordinary skill in the art would go about determining an amount of the claimed active agent (see structure *supra*) that would, in fact, be therapeutically effective to treat Creutzfeldt-Jakob disease without requiring the skilled artisan to undertake the burden of undue experimentation to do so. The instant specification clearly lacks any discussion as to what factors are assessed to determine if there has been a therapeutic response; what threshold values must be crossed or reactions must be seen to reasonably conclude that a therapeutic response has been achieved; or any approximate or ballpark dosage amounts that would have been reasonably expected to yield a therapeutic response in a subject suffering

from Creutzfeldt-Jakob disease. For example, a medical doctor treating a patient with high blood pressure would reasonably conclude that the administration of an anti-hypertensive drug in an amount that lowered the patient's blood pressure to a normal level would clearly be indicative of a "therapeutically effective amount". However, in the instant case, Applicant has provided no criteria, evidence or reasoning as to any standard by which to measure if a therapeutic response was actually achieved such that the artisan would have been imbued with at least a reasonable expectation of success in readily identifying such an amount(s).

Moreover, the art fails to recognize any standard, let alone any effective, therapies for the treatment of Creutzfeldt-Jakob disease such that the skilled artisan would have been able to measure the therapeutic effect of the claimed therapy against a known and accepted therapy to determine if it was better or worse than what was known in the art at the time of the invention to determine those amounts that were actually "therapeutically effective". It is in this regard that the Creutzfeldt-Jakob Disease Foundation, Inc. ("Creutzfeldt-Jakob Disease and Other Prion Diseases", 2007) is cited for its teachings that, "At the present time, there is no confirmed effective treatment to arrest or cure CJD. The disease is inevitably fatal. The only treatments available for CJD patients focus on easing their symptoms and discomfort. Such measures may include drugs for controlling pain and myoclonus, catheters to collect urine, intravenous fluids, feedings through tubes and frequent repositioning of the patient to avoid bedsores." (p.20)

In light of these teachings, the circumstances not only of determining therapeutically effective dosage amounts, but also of finding therapies that are in any way effective for treating Creutzfeldt-Jakob disease, is highly complex and must take into consideration various factors, most importantly, the pharmacokinetic profile of the drug, the subject to whom it is administered (i.e., age, weight, sex, diet, medical condition of the patient, severity of disease) and physiological differences between subjects being treated. The fact that Applicant fails to set forth any criteria to use as a standard for comparison to

determine what is or is not therapeutically effective; what factors are assessed to determine if there has been a therapeutic response; what threshold values must be crossed or reactions must be seen to reasonably conclude that a therapeutic response has been achieved; and what approximate or even ballpark dosage amounts would be reasonably expected to yield a therapeutic response in a subject suffering from Creutzfeldt-Jakob disease, and in further view of the fact that the art does not recognize any effective therapies for the treatment of the same, is clearly evidence that the state of the art with regard to the determination of a therapeutically effective amount of the claimed active drug (see structure *supra*) to treat Creutzfeldt-Jakob disease was sufficiently complex, unpredictable and elusive that one of skill in the art would not have had a reasonable expectation of success in actually achieving such an objective, absent adequate direction or guidance from Applicant.

It is clear from the discussion presented above that the state of the art with regard to the determination of a therapeutically effective amount of the claimed active agent for the treatment of Creutzfeldt-Jakob disease is highly unpredictable. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification requires more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Applicant provides a single example of the claimed compound in reducing PrPSc concentration *in vitro* in ScN2a cells (Table 1) at three separate concentrations, but fails to discuss how such an example is representative of the claimed method for treating, preventing, inhibiting, reversing or relieving Creutzfeldt-Jakob disease using the same compound *in vivo* in a mammal. While a lack of a working embodiment cannot be a sole factor in determining enablement, the absence of substantial evidence

commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. Nowhere does the specification set forth any guidance or direction as to how one of skill in the art would determine a therapeutically effective amount of the claimed active agent such that the skilled artisan would have been imbued with at least a reasonable expectation of success in determining which amounts would, in fact, elicit a "therapeutic effect" and which amounts would not elicit such an effect. Due to the unpredictable nature of the pharmaceutical arts and the medical arts with respect to the treatment of Creutzfeldt-Jakob disease, in the absence of any guidance or direction as to how the skilled artisan would go about achieving the claimed objective with a reasonable expectation of success, the instant disclosure is viewed as lacking enablement, requiring an undue level of experimentation for this aspect of the invention and clearly not rebutting the presumption of unpredictability in the art at the time of the invention.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Applicant fails to address this unpredictability in the art by providing adequate direction or guidance as to how to practice this aspect of the invention, in terms of disclosing how to determine a therapeutically effective amount of the claimed active agent for the treatment of Creutzfeldt-Jakob disease. As a result, the specification is viewed as lacking an enabling disclosure of the same.

Lack of Enabling Direction to Prevent, Inhibit or Relieve Creutzfeldt-Jakob disease using the Claimed Active Agent

The present claims circumscribe the use and administration of the presently claimed active agent (see structure *supra*) for preventing, inhibiting or relieving Creutzfeldt-Jakob disease. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering a therapeutically effective amount of the claimed active agent that Creutzfeldt-Jakob disease would actually be prevented from developing or worsening or that the progression of the disease could be stopped or reversed. In other words, the skilled artisan would have understood the terms "preventing", "inhibiting" or "relieving", in their broadest reasonable interpretations consistent with MPEP §2111, to mean that the incidence or progression of Creutzfeldt-Jakob disease after administration of the presently claimed active agent would essentially be 0% and could be reasonably expected not to develop, occur, recur or worsen. In light of the fact that the specification fails to provide the skilled artisan with any direction or guidance as to how such objectives could actually be achieved, since the disclosure is solely directed to the concept of treatment in patients that already exhibit PrPSc characteristic of Creutzfeldt-Jakob disease and are diagnosed with the same, the present specification is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the prevention, inhibition or relief of Creutzfeldt-Jakob disease, the objective truth that the development of Creutzfeldt-Jakob disease could be prevented from occurring or that progression of the disease could be stopped or reversed is doubted because the state of the art with regard to the definitive prevention, inhibition of or relief from such a disease (i.e., the prevention of developing or worsening or the reversal of Creutzfeldt-Jakob disease) is grossly underdeveloped and such objectives are not recognized in the art as possible to achieve.

The objective truth of the statement that Alzheimer's disease may be prevented from occurring or that progression of the disease could be stopped or reversed is doubted because the disease is particularly

elusive and manifests itself in a variety of different ways in different subjects such that the diagnostician cannot be sure that the disease is truly the cause of the signs and symptoms of disorder exhibited by the patient. A diagnosis of Creutzfeldt-Jakob disease is tentative, at best, until the diagnosis can be confirmed by the neuropathological features found in the brain at autopsy.

Such difficulties in diagnosis are recognized in the art. Applicant's attention is drawn to Knight R ("Creutzfeldt-Jakob disease: Clinical Features, Epidemiology and Tests", *Electrophoresis*, 1998, 19:1306-1310), which states, "There are a number of particularly important areas of uncertainty in the study of CJD (listed in Table 3). The recognition of an illness in a basic step in its management and study, but purely clinical diagnosis (*i.e.*, based on the history and routine examination alone) is either not possible or not very reliable for many diseases. Diagnostic tests are therefore generally sought to support clinical opinions. The *in vivo* diagnosis of CJD is important for surveillance and obviously extremely helpful to clinicians and relatives. Typical cases of CJD may be suspected on clinical grounds but there are other neurological illnesses which may present with similar features and atypical cases also occur. The neuropathological features of CJD are characteristically unique and thus examination of cerebral tissue provides a firm foundation to the diagnosis of the disease. Autopsy is the only way of obtaining the whole brain for detailed examination but, by definition, is not an *in vivo* procedure and permission for autopsy may not be granted. Cortical biopsy can be undertaken in life but is an invasive procedure that carries potential risk to both the patient and the medical personnel. In addition, it may not always provide a clear answer, depending on the anatomical distribution of the pathological changes at the time it is undertaken." (para. bridging p.1308-1309 and Table 3 at p.1309)

In this regard, it is also noted that the art fails to recognize any effective therapies, let alone cures, for Creutzfeldt-Jakob disease, see in particular, Creutzfeldt-Jakob Disease Foundation, Inc. ("Creutzfeldt-Jakob Disease and Other Prion Diseases", 2007), which teaches that, "At the present time, there is no confirmed effective treatment to arrest or cure CJD. The disease is inevitably fatal. The only treatments

available for CJD patients focus on easing their symptoms and discomfort. Such measures may include drugs for controlling pain and myoclonus, catheters to collect urine, intravenous fluids, feedings through tubes and frequent repositioning of the patient to avoid bedsores." (p.20) Furthermore, there are only certain criteria recognized in the art as providing a definitive diagnosis of the disease, see in particular, Creutzfeldt-Jakob Disease Foundation, Inc. ("Creutzfeldt-Jakob Disease and Other Prion Diseases", 2007), which teaches that examination of the brain after death is the only way to diagnose CJD with certainty (p.19). However, Creutzfeldt-Jakob Disease Foundation, Inc. teaches that histological examination, PrP immunohistochemical examinations, Western blots and genetic analysis may also provide some information conducive to making a diagnosis, but further discloses that, "The difficulties involved in diagnosing CJD may have prevented the identification of the disease in some cases. Since the disease progresses rapidly, the patient may die before a diagnosis can be made. Furthermore, some physicians may not even consider the possibility of a CJD diagnosis because the disease is deemed to be rare and the clinical symptoms of CJD can often be attributed to other ailments. Consequently, CJD may be mistaken for a variety of psychological illnesses and other neurological disorders like Alzheimer's Disease, Pick's Disease, Huntington's Disease, cerebral hematomas and vascular irregularities. The extent to which such misdiagnosis may have occurred is presently unknown." (p.19-20)

Given that there a only a few factors that are recognized to have moderate, if any, predictive value in determining the likelihood that patients develop such a disease or to even determine whether patients actually have such a disease, since many of the early signs of Creutzfeldt-Jakob disease are common complaints of other neurological and/or neurodegenerative conditions, such as Alzheimer's disease (see Creutzfeldt-Jakob Disease Foundation, Inc., p.19-20), one of ordinary skill in the art would not accept on its face Applicant's statement that the onset of Creutzfeldt-Jakob disease could be prevented and/or inhibited, stopped or reversed using the presently claimed active agent. In fact, such complexity of diagnosis precludes a common, art-accepted protocol for preventing, let alone inhibiting, stopping or

reversing, Creutzfeldt-Jakob disease in any patient, given that the circumstances or risk factors are unique to that individual and must be considered on a case-by-case basis when determining the most effective approach to preventing Creutzfeldt-Jakob disease from developing or even worsening.

In other words, not only is the population in need of such treatment not particularly well defined in the art because of the difficulties associated with making an accurate diagnosis, but the disease is also sufficiently complicated and poorly understood such that the idea that any active agent (including that presently claimed) would be capable of preventing the onset of (or even curing) such a condition via administration of the presently claimed active agent would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the population of patients in need of such prevention, inhibition, reversal or cure could be identified and how the presently claimed active agent could actually prevent, inhibit, stop or reverse Creutzfeldt-Jakob disease such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of Creutzfeldt-Jakob disease would have been unique and, thus, met with a great deal of skepticism.

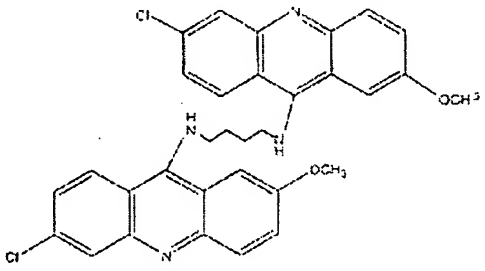
It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides a single example of the claimed compound in reducing PrPSc concentration *in vitro* in ScN2a cells (Table 1) at three separate concentrations. However, none of these studies demonstrates the ability of the claimed active agent to effectively prevent, inhibit, stop or reverse Creutzfeldt-Jakob disease. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compounds for achieving the objective of preventing, inhibiting, stopping or reversing Creutzfeldt-Jakob disease. Nowhere does the specification disclose the manner or procedure of using the presently claimed active agent for preventing the onset of Creutzfeldt-Jakob disease such that the skilled artisan would have been imbued with at least a reasonable expectation of success in determining those patients in need of prevention of Creutzfeldt-Jakob disease without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the

manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objectives of treating (defined as also encompassing the embodiments of prevention, inhibition or relief; see, e.g., p.11-12, para.[0060-0063]; p.25, para.[00100]) Creutzfeldt-Jakob disease in a patient that has, or is at risk for, said disease using the bis-cyclic compound  in a therapeutically effective amount could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1, and the claims dependent therefrom, are directed to a method for treating disease resulting from malformed proteins from a mammal comprising administering to said mammal a therapeutically effective amount of a bis-cyclic compound, wherein said bis-cyclic compound is characterized by clearing malformed proteins and by an ability to cross a blood brain barrier of said mammal.

In particular, it is noted that present claims 1-14 read upon a "method for treating disease resulting from malformed proteins", but Applicant has failed to connect the preamble objective of treating the disease resulting from malformed proteins to the mammal actually being treated by the method. For example, it is not clear whether the subject is actually suffering from a disease resulting from malformed proteins or whether the method is intended for practice in any patient who may or may not have such a disease associated with malformed proteins. In other words, Applicant has not made clear on the record whether the mammal is one in need of treatment of a disease resulting from malformed proteins.

For these reasons, the metes and bounds of the present claims cannot be identified and one of ordinary skill in the art would not necessarily be reasonably apprised of the scope of the claims. In light of such, claims 1-14 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1, and the claims dependent therefrom, are directed to a method for treating disease resulting from malformed proteins from a mammal comprising administering to said mammal a therapeutically effective amount of a bis-cyclic compound, wherein said bis-cyclic compound is characterized by clearing malformed proteins and by an ability to cross a blood brain barrier of said mammal.

Applicant's attention is directed to the MPEP at §2173.05(c)(III), which stated, "The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954)."

Regarding the limitation "a therapeutically effective amount" (claim 1), the recitation of such an

effective amount fails to delineate the function of the effective amount. It is necessarily implied from the present claims as written that the amount of the bis-cyclic compound is intended for use to elicit a therapeutic effect. However, it is not clear as to what condition(s), disease(s) or disorder(s) of the host upon which the combination is capable of exerting such a therapeutic effect and/or what effect is, in fact, achieved by the "therapeutically effective amount". Applicant's failure to define for what the amount of the claimed bis-cyclic compound is therapeutically effective renders the claim vague and indefinite because the skilled artisan would not have been reasonably apprised of the intended function of the therapeutic amount of the claimed active agent. Accordingly, Applicant has failed to clearly delineate the metes and bounds of the subject matter for which Applicant is presently seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the publications to Girault et al. ("Antimalarial, Antitrypanosomal, and Antileishmanial Activities and Cytotoxicity of Bis(9-amino-6-chloro-2-methoxyacridines): Influence of the Linker", *J. Med. Chem.*, 2000, 43:2646-4654); Korth et al. ("Acridine and Phenothiazine Derivatives as Pharmacotherapeutics for Prion Disease", *PNAS*, 98(17):9836-9841); and May et al. ("Potent Inhibition of Scrapie Prion Replication in Cultured Cells by Bis-Acridines", *PNAS*, Published March 18, 2003, E-Published March 7, 2003; 100(6):3416-3421; Abstract and Full Text).

Rejection of claims 1-15 is proper.

Claims 16-28 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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August 1, 2007

8/5/07
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